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Psychotropic Drugs as Negative Reinforcers*

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Introduction

SCHEDULED injections of opiates, amphetamines, barbiturates, and minor tranquilizers can maintain responding in different species (6–9, 12–14); that is, these drugs can function as positive reinforcers. Similarly scheduled injections of some hallucinogens, major tranquilizers, and some opiate antagonists have failed to maintain behavior. Indeed, these drugs often suppress responding that results in their injection. That some of these drugs could function as negative reinforcers was first shown by Goldberg *et al.* (5–7) who found that morphine-dependent rhesus monkeys would respond to terminate infusions of opiate antagonists or stimuli associated with such infusions. It remained an open question, however, whether responding was engendered and maintained only because these antagonists precipitated the morphine-withdrawal syndrome under these conditions. Subsequently, Hoffmeister and Wuttke (10) found that responding could be maintained in nondependent rhesus monkeys under similar schedules of termination with nalorphine and cyclazocine, but not naloxone. They concluded that nalorphine and cyclazocine could function as negative reinforcers even under conditions in which they did not precipitate withdrawal.

The purpose of the experiments reviewed here was to determine whether infusions of the psychotropic drugs, LSD (lysergic acid diethylamide), STP [1-(2, 5-dimethoxy-4-methyl-phenyl) 2-propylamine-hydrochloride], chlorpromazine or imipramine would function as negative reinforcers in the rhesus monkey. The effects of these drugs in maintaining responding that terminated either their infusion or stimuli associated with such infusion were compared with the effects of these drugs on responding maintained by comparable schedules of termination of electric shock.

Procedure

After being surgically prepared with chronic venous catheters and subcutaneous electrodes, the monkeys were placed in individual cubicles where they lived for the duration of the experiment. Details of the apparatus and the catheterization procedure have been reported by Deneau *et al.* (4). Food and water were freely available. To prevent tuberculosis, monkeys received 10 mg of isoniazid per kg daily.

After recovery from surgery (2 weeks), the monkeys were trained to press a lever which turned off a white light associated with the delivery of electric shocks of 10 sec duration (American Electronics Laboratories stimulator 104; 50 Hz, 7V for 1 msec). Shocks were scheduled to occur 30 sec after the light came on or 30 sec after the end of the previous shock; a response turned off the light and the electric shock (if one was being delivered) for a 60-sec time-out period. During time-out periods electric shocks were never delivered, and responses had no scheduled consequences. A session of 2 hr duration was conducted daily with each monkey.

When the monkeys responded reliably within 30 or 40 sec after the white light came on for several daily sessions, electric shocks were no longer delivered. Respond-

*Parts of these experiments have been submitted to Journal of Pharmacology and Experimental Therapeutics for publication.

ing ceased within 2 weeks. After this extinction period, 10-sec infusions of saline solution were scheduled in the same way that electric shocks had been scheduled previously. During this period some responding occurred as the monkeys became accustomed to the noise of the infusion pumps. When responding ceased again, 10-sec drug infusions were scheduled in the same way that saline had been scheduled previously. Each dose of a drug was studied for 6 or 12 successive daily 2-hr sessions. Each drug period was always followed by a saline period which continued until the subjects again showed little responding (6 to 14 days). The number of saline infusions tolerated by each monkey during the last 6 days of each saline period served as control. Then, saline was replaced again by the next dose of the drug being studied. Each dose of any drug was studied in three to six different monkeys. The different doses of each drug were studied in decreasing sequence always starting with the highest. For assignment of drugs and doses to monkeys no strict rule was observed. The data were analyzed as follows:

1. Number of drug infusions tolerated was calculated as percent of the number of saline infusions tolerated by the same subject. Since the volume of the solution administered depended upon the number of responses which terminated infusions, the number of infusions were estimated by dividing the total intake in milliliters per session by 0.8 ml (volume of one complete infusion).

2. Mean number of responses per 2-hr session in the presence of the white light was calculated for each 3 days of the drug period. (Time-out responses are not included in the calculation but appeared on the cumulative record.)

3. Total drug intake in milligrams per kilogram per session.

In a second group of experiments, five monkeys used in the experiments described above were trained again under the schedule in which responding terminated a stimulus associated with 10-sec electric shocks [American Electronics Laboratories stimulator 104; 50 Hz, 7V (1 animal) or 2.7V (4 animals) for 1 msec]. The electric shock intensity was adjusted to produce comparable behavioral reactions in each monkey.

The monkeys were treated with drugs only when performance had been stable during three successive daily 2-hr sessions. Drugs were administered intravenously either 15 min before the session (nalorphine, imipramine, chlorpromazine) or just before the session (LSD, STP, pentobarbital). The data were analyzed as follows:

1. Number of shocks tolerated during each session.

2. Number of responses per 2-hr session in the presence of the white light. (Time-out responses are not included in the calculations.)

Chlorpromazine, imipramine, pentobarbital, LSD, STP, or nalorphine were dissolved in saline solutions; all doses refer to the base (pentobarbital: acid) of the drug. Each dose was studied in three monkeys.

Results

During the initial period of training under the schedule of termination of electric shock, responding was engendered and maintained; the monkeys received few electric shocks (fig. 1A). After the electric shocks had been eliminated and subsequently replaced by 10-sec infusions of saline, responding ceased (fig. 1B). When infusions of 2.5 μg of LSD per kg were substituted for saline, many successive infusions occurred before responding was engendered and maintained (fig. 1C). In subsequent sessions, responding was maintained; the few infusions that did occur were quickly terminated (fig. 1D). Again, the substitution of saline infusions for LSD infusions resulted in very low levels of responding (fig. 1E).

The results obtained with infusions of LSD are summarized in figure 2A–C. The number of tolerated infusions of LSD was inversely related to the dose (fig. 2A),

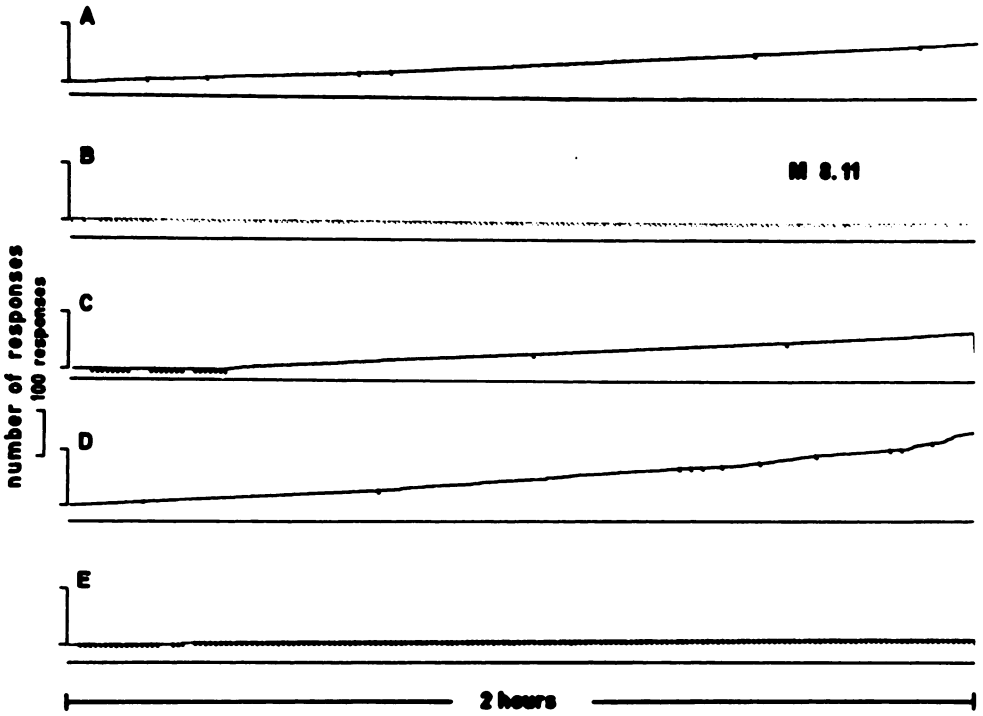

FIG. 1. Representative performance of monkey 8.11 pressing a key under schedules of termination of a stimulus associated with electric shock (A); with infusions of saline solutuon (B and C); or with infusions of 2.5 μg of LSD per kg (C and D). Electric shocks or infusions of 10-sec duration were scheduled to occur every 30-sec in the presence of a white light. Each response terminated the white light and the shock or the infusion (if one had started) for a 60-sec time-out period, in which key pressing had no scheduled consequences, and shocks or infusions were never delivered. Ordinates; cumulative number of responses; short-diagonal strokes indicate periods in which the recording pen was offset during delivery of electric shocks (A) or drug infusions (B to E); abscissae; time; the recorder continued to run during time-out periods (2-hr session). Record A: Session under the electric shock schedule. Record B: Third session of saline infusion. Record C: First session of LSD infusion (2.5 μg/kg per infusion). Record D: Fourth session of LSD infusion (2.5 μg/kg per infusion). Record E: Third session after saline solutions were substituted for LSD infusions.

whereas number of responses was directly related to the dose (fig. 2B). Responding was maintained throughout the 6-day drug period with infusions of 2.5 μg/kg, maintained only during the second half of the drug period with 1.0 μg/kg, and only poorly maintained by 0.5 μg of LSD per kg. The maximum intake of LSD was about 0.1 mg/kg per session with infusions of 1.0 μg/kg (fig. 2C).

The effects of LSD on responding maintained by termination of a stimulus associated with electric shock is shown in figure 2D. Pretreatment with 50 μg of LSD per kg intravenously immediately before the session had no influence on responding. Increasing the LSD dose to 125 and 250 μg/kg intravenously caused a small but dose-dependent decrease in number of responses and a corresponding increase in number of shocks. This effect occurred mainly during the first 10 to 30 min of experimental sessions (fig. 3). With 1 to 5 μg/kg, responding diminished during the first 10 min; with 250 μg/kg, responding diminished during the first 30 min of the session. After these periods, responding was unaffected, thereby indicating the short duration of action of LSD.

Stimuli associated with the infusions of nalorphine also engendered and maintained avoidance responding [fig. 4; see also Hoffmeister and Wuttke (10)]. Doses as low as 10 μg/kg reduced the number of

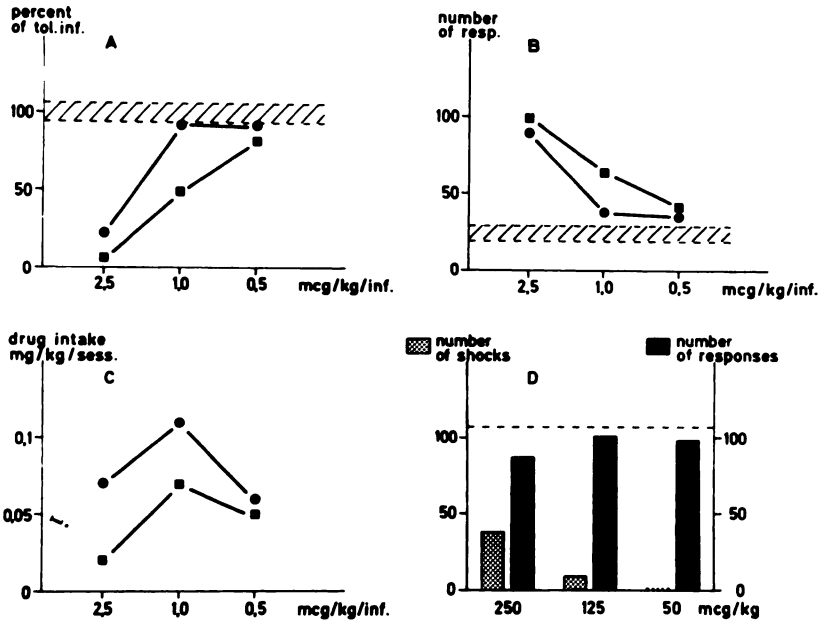

FIG. 2. A-C: Effects of varying infused dose of LSD on the percentage of infusions tolerated, number of responses, and drug intake during the first and second half of the six-session drug period. D: Effects of LSD on mean number of responses and electric shocks per session under the schedule of termination of a stimulus associated with electric shock. Circles indicate means of first half of drug period; squares indicate means of second half of drug period; horizontal dashed lines indicate confidence limits of saline infusions tolerated and number of responses with saline infusions.

tolerated infusions (fig. 4A) and increased responding (fig. 4B). The maximal intake of nalorphine was about 3.5 mg/kg per session with infusions of 500 μg/kg (fig. 4C). In contrast to LSD, which at least for a short time decreased rate of responding maintained by termination of a stimulus associated with electric shock, nalorphine, in doses up to 10,000 μg/kg, did not affect responding or number of shocks tolerated in the shock termination experiment (fig. 4D).

Infusions of the hallucinogenic STP, in the range of doses tested, were less effective in engendering responding than infusions of LSD or nalorphine (fig. 5). With 2.5 μg/kg per infusion the animals tolerated 50% of the scheduled infusions. There was no change when the dose was increased to 5 μg/kg (fig. 5A). Number of responses was moderately increased from saline levels at doses of 2.5 or 5 μg/kg (fig. 5B). The maximal drug intake per session was about 2.5 mg/kg with infusions of 5 μg/kg (fig. 5C). As with nalorphine, pretreatment with STP in doses up to 1000 μg/kg did not affect responding maintained by termination of a stimulus associated with electric shock (fig. 5D).

Infusions of chlorpromazine in the dose range of 1 to 20 μg/kg per infusion during the first 3 days of the drug period only decreased low levels of responding that had been maintained with saline and increased tolerated infusions above the saline level (fig. 6A). During the second 3 days of the drug period, infusions of 5 to 20 μg of chlorpromazine per kg engendered responding and decreased the percentage of tolerated infusions to 50 or 60% of saline-level values (fig. 6A, B). The maximal drug intake was about 7.0 mg/kg per session at 50 μg/kg (fig. 6C). Responding maintained by termination of a stimulus associated with electric shock was markedly decreased by pretreatment with doses as low as 250 μg of chlorpromazine per kg (fig. 6D); increasing the dose of chlorpromazine to 500 or 5000 μg/kg suppressed responding completely (fig. 6D).

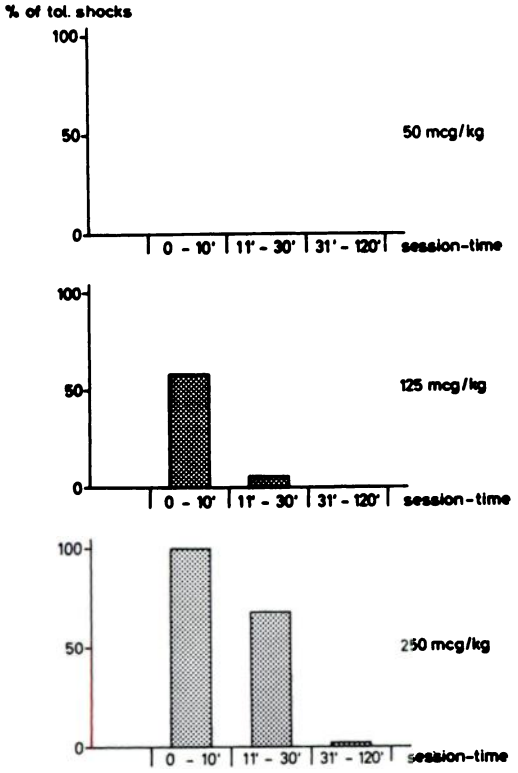

FIG. 3. Effects of LSD on mean percentage of tolerated electric shocks during successive segments of the 2-hr session.

Since responding was slow to develop and not well maintained by termination of a stimulus associated with infusions of chlorpromazine, an experiment with an extended exposure to chlorpromazine was performed. Figure 7 represents the time course of this experiment. The number of tolerated infusions decreased from the 9th to the 12th day of replacement to less than 10% of the saline level, and responding increased markedly from the 4th day of the drug period on.

Infusions of imipramine, in the range of doses tested, did not engender responding; the animals tolerated all infusions with the exception of 50 μg/kg (fig. 8). The maximal drug intake per session was 10 mg/kg at the dose of 100 μg/kg. Responding maintained by termination of a stimulus associated with electric shock was little affected by 5000 μg of imipramine per kg (fig. 8D). However, increasing the dose of imipramine to 10,000 or 16,000 μg/kg increased the number of shocks and decreased the number of responses in a dose-dependent fashion.

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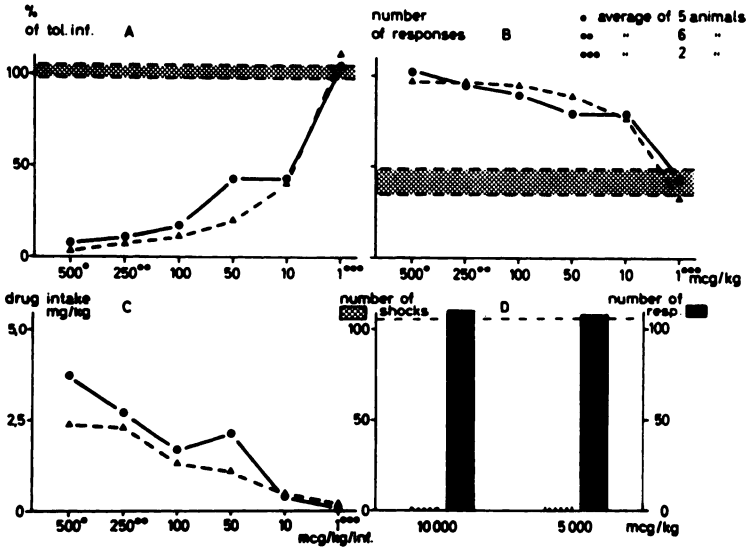

FIG. 4. A–C: Effects of varying infused dose of nalorphine on the percentage of infusions tolerated, number of responses, and drug intake during the first and second half of the six-session drug period. D: Effects of nalorphine on mean number of responses and electric shocks per session under the schedule of termination of a stimulus associated with electric shock. Circles indicate means of first half of drug period; squares indicate means of second half of drug period; horizontal dashed lines indicate confidence limits of saline infusions tolerated and number of responses with saline infusions.

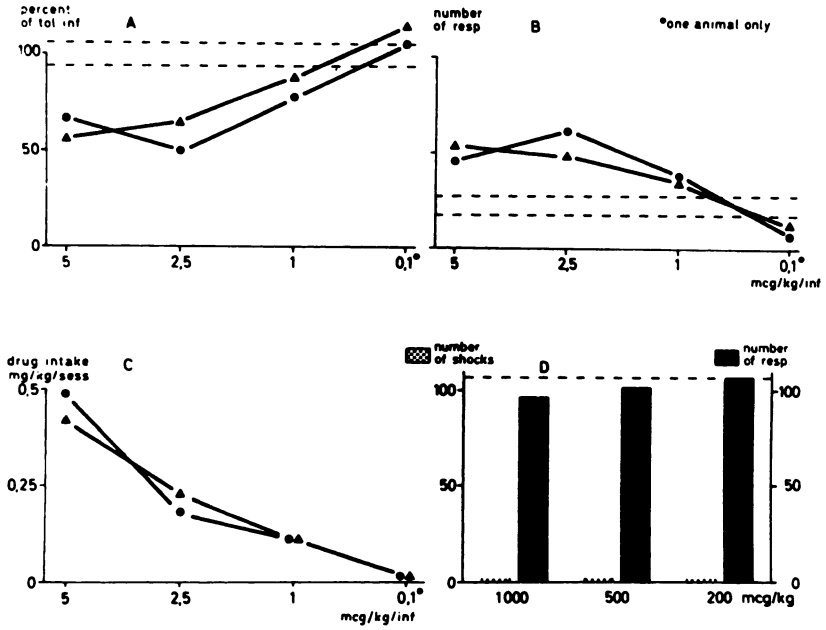

FIG. 5. A–C: Effects of varying infused dose of STP on the percentage of infusions tolerated, number of responses, and drug intake during the first and second half of the six-session drug period. D: Effects of STP on mean number of responses and electric shocks per session under the schedule of termination of a stimulus associated with electric shock. Circles indicate means of the first half of drug period; squares indicate means of second half of drug period; horizontal dashed lines indicate confidence limits of saline infusions tolerated and number of responses with saline infusions.

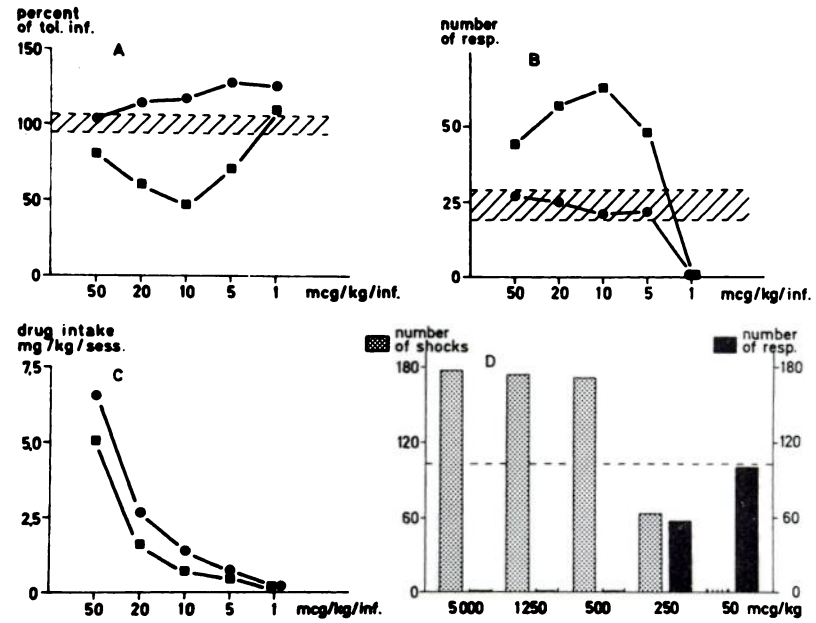

FIG. 6. A–C: Effects of varying infused dose of chlorpromazine on the percentage of infusions tolerated, number of responses, and drug intake during the first and second half of the six-session drug period. D: Effects of chlorpromazine on mean number of responses and electric shocks per session under the schedule of termination of a stimulus associated with electric shock. Circles indicate means of the first half of drug period; squares indicate means of second half of drug period; horizontal dashed lines indicate confidence limits of saline infusions tolerated and number of responses with saline infusions.

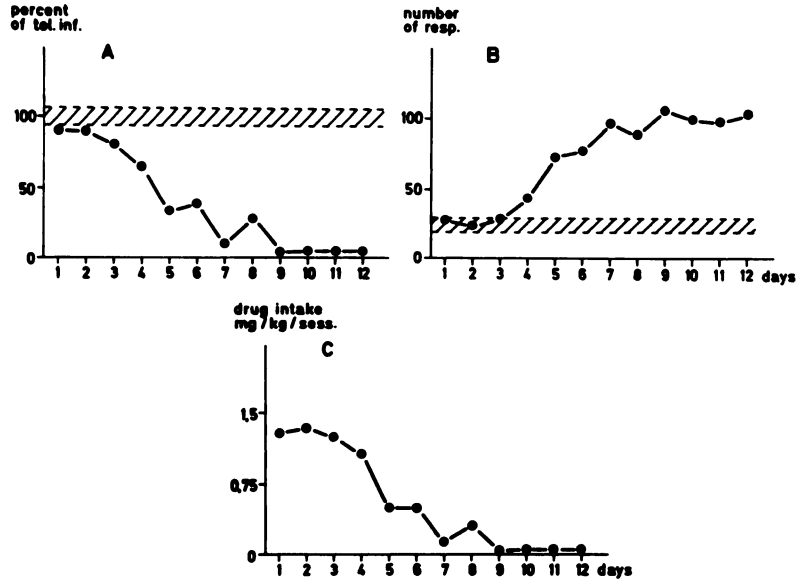

FIG. 7. Effects of chlorpromazine (10 μg/kg per infusion) on the percentage of infusions tolerated, number of responses, and drug intake in each session of a 12-day drug period. Horizontal dashed lines indicate confidence limits of saline periods.

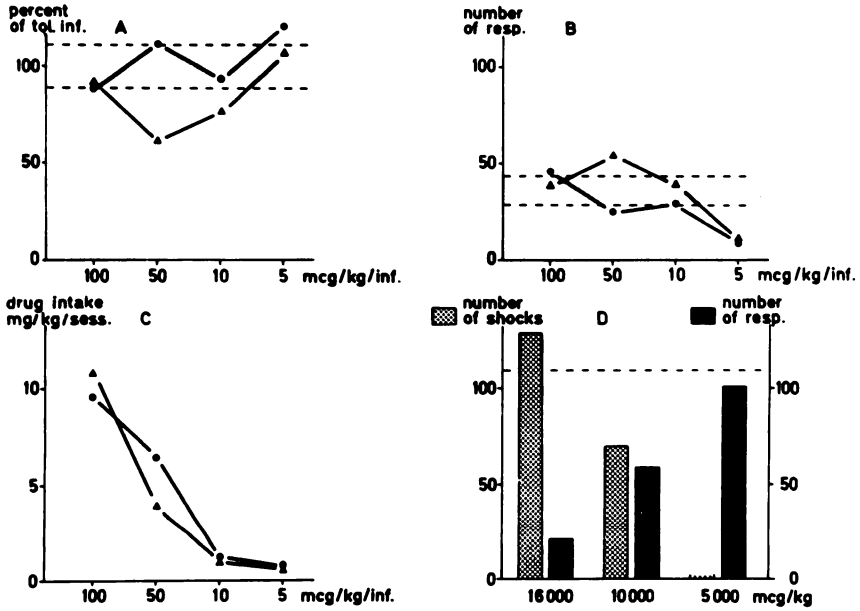

FIG. 8. A-C: Effects of varying infused dose of imipramine on the percentage of infusions tolerated, number of responses, and drug intake during the first and second half of the six-session drug period. D: Effects of imipramine on mean number of responses and electric shocks per session under the schedule of termination of a stimulus associated with electric shock. Circles indicate means of first half of drug period; squares indicate means of second half of drug period; horizontal dashed lines indicate confidence limits of saline infusions tolerated and number of responses with saline infusions.

maintained by termination of imipramine during the first 3 days of the drug period infusions were similar to those previously observed with chlorpromazine, prolonged exposures to the 50 and 100 μg doses of imipramine per kg were studied. With infusions of 50 μg of imipramine per kg, responding showed small increases be-

tween the 4th and 7th sessions but decreased again in subsequent sessions; similarly, the number of tolerated infusions decreased between the 4th and 7th session, but increased again in subsequent sessions (fig. 9). In an identical experiment with infusions of 100 μg/kg, the animals tolerated almost every imipramine infusion throughout the 12-day drug period (fig. 9).

Infusions of 10 or 100 μg of pentobarbital per kg did not engender responding and even more pentobarbital than saline infusions were tolerated (fig. 10). The highest drug intake was 15 mg/kg per session at the dose of 100 μg/kg (fig. 10C). Responding maintained by termination of a stimulus associated with electric shock was little affected by 1,250 or 10,000 μg of pentobarbital per kg, but was markedly decreased by 15,000 μg of pentobarbital per kg (fig. 10D).

Discussion

Our experiments have shown that responding can be engendered and maintained in drug naive rhesus monkeys by termination of a stimulus associated with infusions of LSD, nalorphine, STP, or chlorpromazine; thus, these drugs can act as negative reinforcers. Under the same schedules of termination, little responding was engendered by infusions of imipramine and none by infusions of pentobarbital. Doses of LSD or chlorpromazine that engendered responding under the schedule of termination of stimuli associated with infusions decreased or abolished responding under a comparable schedule of termination of a stimulus associated with electric shocks. The respective doses of nalorphine, STP, and imipramine had no effect on behavior under the electric shock schedule. Pentobarbital, which did not engender responding under the drug-infusion schedule, decreased rates of responding under the electric shock schedule.

These results show that intravenous infusions of certain psychotropic drugs can function as negative reinforcers in drug-naive rhesus monkeys. The capacity of a drug to act as a negative reinforcer seems to be independent of the influence that the drug exerts on behavior maintained by another event, such as electric shock, acting as a negative reinforcer. Chlorpromazine or LSD, for example, can function as

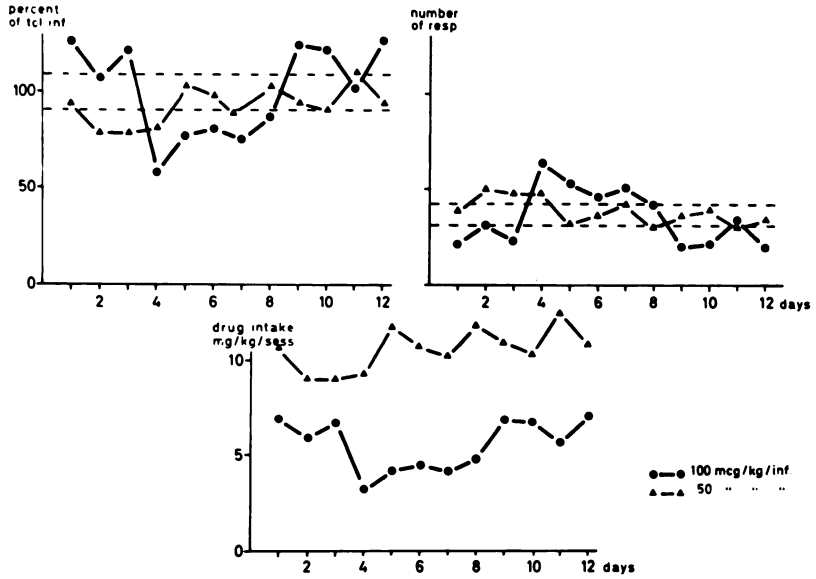

FIG. 9. Effects of imipramine (50 and 100 μg/kg per infusion) on the percentage of infusions tolerated, number of responses, and drug intake in each session of a 12-day drug period. Horizontal dashed lines indicate confidence limits of saline periods.

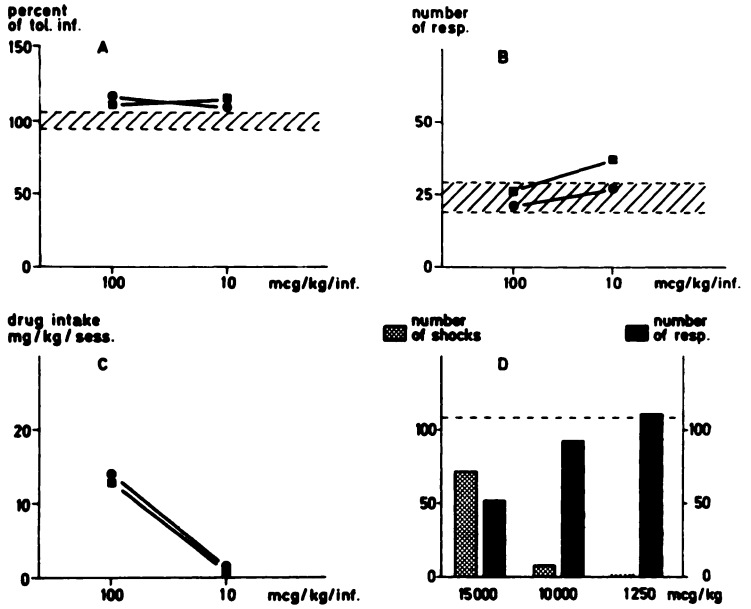

FIG. 10. A-C: Effects of varying infused dose of pentobarbital on the percentage of infusions tolerated, number of responses, and drug intake during the first and second half of the six-session drug period. D: Effects of pentobarbital on mean number of responses and electric shocks per session under the schedule of termination of a stimulus associated with electric shock. Circles indicate means of first half of drug period; squares indicate means of second half of drug period; horizontal dashed lines indicate confidence limits of saline infusions tolerated and number of responses with saline infusions.

negative reinforcers to engender and maintain responding despite the strong rate-decreasing effects of these drugs on responding maintained by electric shock as a negative reinforcer (see also 1-3, 11). Both STP and nalorphine can function as negative reinforcers at doses that do not affect responding under the electric shock schedule.

The negative reinforcing effects of chlorpromazine became apparent only after a period of 2 to 4 days. During the first 3 days of the drug period, the animals tolerated all doses of chlorpromazine. During the second 3 days, the development of responding resulted in a dose-dependent decrease in infusions tolerated. The number of tolerated infusions decreased further with prolonged exposure to the drug. As can be seen from the dose-effect curves, the initiation of responding is most prominent at intermediate dose levels.

That infusions of relatively high doses of chlorpromazine (50 μg/kg per infusion; 5 to 7 mg/kg per session) are less effective in engendering responding than lower doses cannot be explained only by long-lasting rate-depressing and sedative effects. The effects of doses of up to 5 mg/kg on responding maintained under the electric shock schedule do not last longer than 4 to 10 hr. Thus, under the drug infusion schedule, the rate depressing effects of chlorpromazine injected in one session should not affect responding in the next session. The rate-depressing effect of LSD lasted only for a short time as shown in the electric shock schedule; thus, the possibility of a carry-over of this effect from one session to the next under the drug infusion schedule can also be excluded. The reason for the delayed development of responding in the drug infusion experiment remains to be explained.

Interestingly, imipramine does not function well as a negative reinforcer, and it has only weak rate-depressing properties under the electric shock schedule. Since imipramine was also found not to function as a positive reinforcer (8), it is the only psycho-

tropic drug so far investigated which seems not to have the capacity to function as a reinforcer at all.

In summary, infusions of psychotropic drugs can act as reinforcers independently of their effects on behavior engendered and maintained by other reinforcers.

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